REMARKS

In the last Office Action, the Examiner rejected claims 12 and 27 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 4,191,182 to Popovich et al. ("*Popovich*") in view of U.S. Patent No. 4,906,375 to Heilmann et al. ("*Heilmann*"); rejected claims 13 and 28 under 35 U.S.C. § 103(a) as being unpatentable over *Popovich* in view of *Heilmann* and further in view of U.S. Patent No. 4,435,289 to Breslau ("*Breslau*"); rejected claims 14, 15, 29, and 30 under U.S.C. § 103(a) as being unpatentable over *Popovich* in view of *Heilmann* and further in view of U.S. Patent No. 6,572,641 to Brugger et al. ("*Brugger*"); and rejected claims 14, 15, 29, and 30 under U.S.C. § 103(a) as being unpatentable over *Popovich* in view of *Heilmann* and *Breslau* and further in view of *Brugger*.

REJECTION UNDER § 103(a)

In the Office Action, the Examiner rejected claims 12 and 27 under 35 U.S.C. § 103(a) as being unpatentable over *Popovich* in view of *Heilmann*. Applicant respectfully traverses this rejection. Applicant submits that *Popovich* and *Heilmann* do not disclose a method wherein "a water permeability coefficient L_pA of the filter is at least 10 ml/min/mm Hg; [and] the cleaning fluid flow rate is at least 1000 ml/min," as recited in independent claim 12, or a device having a filter with the same water permeability characteristic and that is configured to sustain a cleaning fluid flow rate of at least 1000 ml/min to the filter," as recited in independent claim 27.

When considering a Section 103 rejection, "a prior art reference must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the claimed invention." M.P.E.P. 2141.02(VI), (emphasis added). Furthermore, while the nature of the teaching must be weighed, "[a] prior art reference that 'teaches away' from the claimed invention is a significant factor to be considered in determining obviousness." M.P.E.P. 2145(X)(D)(I), (emphasis added).

Popovich discloses "[a] process and apparatus . . . for continuously separating blood into plasma and cellular component fractions and returning the latter to the subject in admixture with a makeup fluid." (Abstract.) *Popovich* further discloses an ultrafiltration cell with an ultrafiltration membrane 11. (See col. 6, lines 38-43.) The Examiner contends that "Popovich et al further teach that the replacement fluid rate (e.g. cleaning fluid) can be from 75 ml/min to 600 ml/min since recycle flow rate is maintained in the range from about 5 ml/minute/layer to about 40 ml/min/layer in 15 separate ultrafiltering membrane layers." (Office Action at 2.) The Examiner concedes that "[c]laims 12 and 27 essentially differ from the method and apparatus of Popovich et al in reciting a water permeability coefficient of the filter being at least 10 ml/min/mmHg and the cleaning fluid flow rate being at least 1000 ml/min." (Office Action at 3.) However, the Examiner further contends that "[i]t would have been obvious to one having ordinary skill in the art at the time the invention was made to optimize the flow rate of [the] cleaning fluid, since it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art." (Office Action at 3.) Applicant respectfully disagrees.

As an initial matter, the general conditions of Applicant's claim are not disclosed in the prior art. Claim 12 recites, for example, "the cleaning fluid flow rate is at least 1000 ml/min." Claim 27 recites that "the device is configured to sustain a cleaning fluid flow rate of at least 1000 ml/min to the filter." In Applicant's published specification, Applicant notes that the invention "is accomplished by a simultaneous significant increase of the flow rate of the dialysis fluid and of the area of the membrane that separates the blood from the dialysis fluid, compared to conventional dialysis." (Abstract.) Applicant also states that the flow rate used in the invention "may be 10 times higher than normal." (Specification ¶ [0035].) In other words, the flow rates used in Applicant's invention are much higher than the flow rates used in the prior art based on the general conditions known in the prior art.

Furthermore, *Popovich* explicitly teaches away from claims 12 and 27. *Popovich* discloses that:

> [i]n any plasmapheresis-type process effected by ultrafiltration there are various problems which occur during the fractionating of the blood by passing it in a parallel flow pattern over a membrane, with a transmembrane pressure sufficient to push the plasma portion of the blood therethrough, while allowing the cellular component portion of the blood to remain thereon. One of these problems is that the flow rates **must** be controlled fairly closely. Thus, if the flow rate employed is too fast, turbulence will occur within the ultrafiltration cell which may cause hemolysis and the general destruction of cellular components. On the other hand, if flow rates and transmembrane pressures are not controlled adequately the cellular and macromolecular components of the blood will tend to clog up the membrane thus significantly slowing the ultrafiltration rate. Such clogging can also cause hemolysis to occur.

(Col. 2, lines 25-43, emphasis added.)

Popovich also discloses that:

> [f]or the Sartorius cell and membranes described above, recycle flow rates **must** be maintained in the range of from about 5 ml/minute/layer to about 40 ml/minute/layer in order to yield the high shear rates which are necessary to prevent damage occurring to the blood.

(Col. 9, lines 41-45, emphasis added.)

In other words, *Popovich* discloses that flow rates must not be too high. Specifically, *Popovich* teaches that the recycle flow rate, which the Examiner interpreted as corresponding to the "cleaning fluid flow rate" of claims 12 and 27, must be maintained within the range of 5 ml/min/layer to about 40 ml/minute/layer, which the Examiner converted to 75 ml/min to 600 ml/min. Therefore, even assuming, *arguendo*, that the recycle flow rate of *Popovich* corresponds to the cleaning fluid flow rate of claims 12 and 27, which Applicant does not concede, *Popovich* expressly teaches away from "the cleaning fluid flow rate [being] at least 1000 ml/min," as recited in independent claim 12 and "the device [being] configured to sustain a cleaning fluid flow rate of at least 1000 ml/min to the filter," as recited in independent claim 27. Accordingly, it is improper for the Examiner to suggest that it would have been obvious to "optimize" the cleaning fluid flow rate in *Popovich* to be at least 1000 ml/min when *Popovich* explicitly teaches otherwise.

Additionally, *Popovich* deals with plasmapheresis. In plasmapheresis, the maximum size of the substances removed is large, which results in most of the large blood proteins also being removed (including albumin with a MW of about 66 000, but also globulins and the like which are more than 10 times larger). The liquid volume and

these proteins need to be replaced using a replacement fluid. Most often, fresh frozen plasma is used as a replacement fluid. Due to immunological reasons, the allowed volume of replacement fluid per treatment is limited (e.g., normally less than 4 liters, but certainly far less than 10 liters). Even if the treatment were to be completed within one hour, which is normally not the case, there would be absolutely no need for a replacement fluid flow rate above 200 ml/min, and the flow rate typically used in plasmapheresis is much smaller than that.

One basic property of plasmapheresis is that it is not just the protein bound solutes that are removed, but the whole protein (albumin) is removed together with all substances bound to it. However, as discussed above, the problem with plasmapheresis is its limited capacity. The instant Application discusses a method to release the protein bound substances from the protein and then transport them away across the membrane (by convection) and out with the effluent ultrafiltrate. As discussed in the Application, this method can be made much more effective than plasmapheresis.

Popovich does not actually discuss any large flow rates of replacement fluid. Fig. 1 of *Popovich* discloses a preferred embodiment where the replacement fluid enters the system via line 33 using pump 31. The flow rate of this replacement fluid is essentially equal to the ultrafiltration rate, which is maintained through line 23 using pump 29. (See col. 7, lines 28-33.) *Popovich* is directed to keeping the recycle flow rates through line 19 high enough using pump 21 to facilitate the necessary ultrafiltration across the membrane. This is to avoid cake formation on the membrane by a sufficient flushing along the membrane surface. (Col. 9, lines 37-45) (pump 21 is explicitly disclosed,

along with the flow rate cited by the Examiner, i.e., 5-40 ml/min/layer along each of up to 15 membrane surfaces).

This flow rate cited by the Examiner, however, has nothing to do with the replacement fluid flow rate (which equals the ultrafiltration rate as discussed above). Instead, typical values for the replacement fluid (or ultrafiltration fluid) can be found in the examples. Table I shows a case where the ultrafiltration rate delivered by the filtrate pump (last column of Table I) varies between 13.8 and 24.3 ml/min with a total volume of 1200 ml during the 60 minute treatment (i.e., an average of 20 ml/min). This differs substantially from the claimed values. For the second example, shown in Table III, the ultrafiltration rates in column 4 are even smaller, between 0.46 and 2.3 ml/min. Accordingly, *Popovich* is not at all relevant to the claimed invention and one of skill in the art would not have combined *Popovich* with *Heilmann* to achieve the claimed invention.

The Examiner relies on *Heilmann* for its alleged disclosure of "hemofiltration membranes having water permeability of about 600 ml/hr/mmHg." (Office Action at 3.) However, *Heilmann* does not remedy the deficiencies of *Popovich* discussed above.

For at least the aforementioned reasons, independent claims 12 and 27 are allowable over the cited reference and the § 103(a) rejection of independent claims 12 and 27 should be withdrawn.

In the Office Action, the Examiner rejected claims 13 and 28 under 35 U.S.C. § 103(a) as being unpatentable over *Popovich* in view of *Heilmann* and further in view of *Breslau*. Applicant respectfully traverses this rejection.

Breslau discloses a "[p]rocess and apparatus for providing separation of solutes, colloidal particles or suspended matter by ultrafiltration[,] wherein increased cost efficiency and reduced energy requirements are realized by series flow configuration." (Abstract.) *Breslau* does not disclose a method wherein "a water permeability coefficient L_pA of the filter is at least 10 ml/min/mm Hg; [and] the cleaning fluid flow rate is at least 1000 ml/min" or a device having a filter with the same water permeability characteristic and that is configured to sustain a cleaning fluid flow rate of at least 1000 ml/min to the filter. Thus, *Breslau* does not remedy the deficiencies of *Popovich* and *Heilmann* described above with regards to claims 12 and 27. Accordingly, the Examiner should withdraw the § 103 rejection of claims 13 and 28 at least due to their dependence from one of independent claims 12 and 27, and due to their additional recitations of patentable subject matter.

Claims 14, 15, 29, and 30 were rejected U.S.C. § 103(a) as being unpatentable over *Popovich* in view of *Heilmann* and further in view of *Brugger*.

Brugger discloses "[a]n external fluid warming device . . . that includes a fluid warming chamber and an air separation chamber." (Abstract.) "The fluid inlet is connected to a source of fluid and the fluid outlet is connected to an output device, such as an ultrafiltration machine." (Abstract.) *Brugger* does not disclose a method wherein "a water permeability coefficient L_pA of the filter is at least 10 ml/min/mm Hg; [and] the cleaning fluid flow rate is at least 1000 ml/min" or a device having a filter with the same water permeability characteristic and that is configured to sustain a cleaning fluid flow rate of at least 1000 ml/min to the filter. Thus, *Brugger* does not remedy the deficiencies of *Popovich* and *Heilmann* described above with regards to claims 12 and

27. Accordingly, the Examiner should withdraw the § 103 rejection of claims 14, 15, 29, and 30 at least due to their dependence from one of independent claims 12 and 27, and due to their additional recitations of patentable subject matter.

Claims 14, 15, 29, and 30 were also rejected U.S.C. § 103(a) as being unpatentable over *Popovich* in view of *Heilmann* and *Breslau* and further in view of *Brugger*.

As noted previously, *Breslau* and *Brugger* do not remedy the deficiencies of *Popovich* and *Heilmann* described above with regards to claims 12 and 27. Accordingly, the Examiner should withdraw the § 103 rejection of claims 14, 15, 29, and 30 at least due to their dependence from one of independent claims 12 and 27, and due to their additional recitations of patentable subject matter.

CONCLUSION

In view of the foregoing remarks, the examiner is respectfully requested to reconsider his position and to timely allow the present application

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account 06-0916.

Respectfully submitted,

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